CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PROPYZAMIDE

Chemical Code #: 000694, Tolerance # 317
SB 950-098

August 7, 1987
Revised 9/28/88, 9/14/90, 4/14/92, 9/20/93, 5/6/94, 6/9/95, 11/9/01, 1/31/05

I. DATA GAP STATUS

Combined, rat:	No data gap, no adverse effects.
Chronic toxicity, dog:	No data gap, no adverse effects.
Oncogenicity, rat:	See combined, rat (above), possible adverse effect.
Oncogenicity, mouse:	No data gap, possible adverse effects.
Reproduction, rat:	No data gap, no adverse reproduction effects[1].
Teratology, rat:	No data gap, no adverse effects.
Teratology, rabbit:	No data gap, no adverse effects.
Gene mutation:	No data gap, no adverse effects.
Chromosomal aberration:	No data gap, no adverse effects.
DNA damage:	No data gap, no adverse effects.
Neurotoxicity:	Not required at this time.

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1 - There is a possible adverse chronic effect in liver (not related to reproduction)
** indicates acceptable study
Bold face indicates possible adverse effect

File name : T050131

Toxicology Summary Revised by H. Green & M. Silva, 9/14/90; Kishiyama & Silva, 4/14/92; Kishiyama & Silva, 9/20/93, Silva, 5/6/94, 6/9/95, 11/9/01, 1/31/05
All studies through volume 0113, record # 215467 have been reviewed.
Toxicology one-liners are attached

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

NOTE: The combined, rat study was performed in two separate phases (chronic and oncogenicity) which were submitted as two studies (060/091888 & 061/091889). Together, the two submissions satisfy the combined rat data requirements (see combined, rat, below).

COMBINED, RAT

025 036797, "Toxicologic Study on the Effect of Adding RH-315 to the Diet of Albino Rats (Two-Year Feeding Study)", (Depart. of Pharmacology, Medical College of Virginia, 6/11/70), combined-835-rat; RH-315, lot no. SW-68-0261, analytical purity 97%, fed in the diet, 30/sex/group, for two years at 0, 30, 100, or 300 ppm; 5/sex/group sacrificed at 6 months for histopathology. No adverse effects reported. NOEL > 300 ppm. UNACCEPTABLE, not upgradable (inadequate number of animals per group, no justification of dose with no NOEL clearly established, no analysis of dose in diet, no tabulation of histopathology, no clinical observations) (Van Way, Remsen (Gee) 11/25/85).

011 961150 Abbreviated version of 036797; (Oshita, Wong, 4/19/85).

060 091888 "Kerb® Herbicide (Technical, no clay): 24-Month Dietary Chronic Toxicity/Oncogenicity Study in Rats", 12-Month Chronic Toxicity Phase, (D. E. Bailey, Hazleton Laboratories America, Inc., HLA Study No. 417-426S, 10/15/90). Kerb* (Technical, no clay, purity = 96.4%) was fed to Charles River rats (Crl:CDBR VAF/PLUS, 20/sex/group) at concentrations of 25, 100, or 400 ppm for the first 2 weeks, then increased to 35, 140, 560 ppm for weeks 3 and 4 and finally adjusted to 40, 200, or 1000 ppm for weeks 5 through week 52. Ten rats/sex/group were terminated at 26 weeks, while the remaining 10/sex/group were treated for 52 weeks. NOEL = 200 ppm (An increase in ketones was observed in males at 1000 ppm. Increased liver/body weight % in both sexes and kidney in males at 1000 ppm. Increased thyroid/parathyroid/brain weight % in females at 1000 ppm. Increased incidence of liver centrilobular hypertrophy in both sexes at 1000 ppm and increased incidence in follicular cell hypertrophy in thyroid in both sexes at 6 months and in females at 12 months at 1000 ppm. B-Follicular cell adenomas were observed in 1 female at 6 months and 1 male at 12 months at 1000 ppm.) Not acceptable as a chronic study. It is only acceptable when combined with data from the rat oncogenicity study 061/091889. Kishiyama & Silva, 3/11/92.

**** 061, 081 091889, 131700** "Kerb® Herbicide (Technical, no clay): 24-Month Dietary Chronic Toxicity/Oncogenicity Study in Rats", 24-Month Oncogenicity Phase, (D. E. Bailey, Hazleton Laboratories America, Inc., HLA Study No. 417-426M, 11/2/90). Kerb* (Technical, no clay, purity = 96.4%) was fed in diet to Charles River Crl:CD*BR VAF/PLUS rats (60/sex/dose) at 0 (vehicle = acetone), 25, 100, or 400 ppm for the first 2 weeks, then increased to 35, 140, 560 ppm for weeks 3-4 and finally to 40, 200, or 1000 ppm weeks 5-105 or 106. Chronic NOEL = 200 ppm/day (Decreased body weight primarily in females and increased relative liver weight in females at 1000 ppm.) Oncogenicity NOEL = 200 (Testes showed increased gross pathology and benign interstitial cell tumors at 1000 ppm. Sertoliform tubular hyperplasia and sertoliform tubular adenomas were observed in ovaries at 1000 ppm. Both sexes had increased centrilobular hypertrophy and eosinophilic alterations in liver and males had increased hepatocellular adenoma and carcinoma at 1000 ppm. Thyroid effects were follicular cell adenoma in both sexes and follicular hyperplasia in females at 1000 ppm.) Acceptable. M. Silva, 6/2/95.

058 091885 & 091886 The discussion in this volume refers to the combined (chronic and oncogenicity) study: "Kerb® Herbicide (Technical, no clay): 24-Month Dietary Chronic

Toxicity/Oncogenicity Study in Rats", (D. E. Bailey, Hazleton Laboratories America, Inc., HLA Study No. 417-426M, 11/2/90). 058/091885 "Perspective on the Increased Incidences of Thyroid and Testicular Tumors Produced by Kerb Herbicide in Rats," states why the registrant believes the increased incidence of adenomas in the rat chronic study occurred by an indirect, non-genotoxic mechanism. Document 058/091886 is a letter from Rohm & Haas Company to EPA that included incidence data for the control and treated groups from the combined study (091888 & 091889) along with historical controls from the laboratory conducting the study. Included in both documents is risk assessment information. These data are supplemental. M. Silva, 3/16/92.

075 128086 "Pronamide (Kerb Herbicide): Effect of Endocrine Regulation on Rat Testes," (Hazelton, G.A., DiDonato, L.J., Kaminski, E.J. and Lomax, L.G., Rohm & Haas Company, PA, 9/24/93; Protocol #: 92P-053, Report #: 92R-053). Propyzamide technical (96.8% pure) was fed in diet to Crl:CD BR male rats at 0 (acetone), 40, 1000, 4000 ppm for 4 or 17 weeks. Another group was treated at 4000 ppm for 4 weeks, followed by a 13-week recovery (30 rats). At 0 & 4000 ppm, there were 60 rats/dose (30 for a 4 & 30 for a 17 week treatment). At 40 & 1000 ppm there were 40 rats/dose (20 for a 4 & 20 for a 17 week treatment). NOEL = 40 ppm (There was a significant decrease in body weight gain at $\geq$ 1000 ppm. LH, FSH and esterone were significantly increased at 4000 ppm. Testes, pituitary and liver weights were significantly increased at $\geq$ 1000 ppm & 4000 ppm. Vacuolation, hypertrophy, and increased LH & FSH activity occurred in the pars distalis of the pituitary. Interstitial cell hypertrophy was observed at 4000 ppm, as was an increase in labelled cells at 17 weeks.) **Possible adverse effect indicated** (interruption in the pituitary-testis endocrine axis occurred at $\geq$ 1000 ppm.) These data are supplemental. M. Silva, 5/6/94.

063 089234 "Kerb® Herbicide (Technical, no clay): 24-Month Dietary Chronic Toxicity/Oncogenicity Study in Rats," Supplement - Histopathology Photomicrographs - 87RC-062K, (Kulwich, B.A. and Harris, J.C., Hazleton Laboratories America, Inc., Vienna, VA, 2/4/91). This volume contains photomicrographs of histopathology from thyroid, liver, testes and ovary from study 091889. No worksheet. M. Silva, 3/17/92.

069 115339, "Pronamide (Kerb® Herbicide): Thyroid Function and Hepatic Clearance of Thyroxine in Male Rats", (G.A. Hazelton, L.J. DiDonato, K.F. Donofrio and B.A. Kulwich, Rohm and Hass Toxicology Department, Report No. 90R-178, 10/9/91). Pronamide (purity = 96.4%) admixed with the feed at concentrations of 0 (acetone mixed with feed), 40, 1000 or 4000 ppm was fed to Crl: CD*BR male rats (20-40/group). Treatment was 4 weeks for half the rats and 15 weeks for those remaining (per group). Also included was a "recovery group" consisting of 20 male rats fed 4000 ppm for 4 weeks and control diet for 11 weeks. NOEL = 40 ppm (Food consumption and body weight were significantly decreased at $\geq$ 1000 ppm. Absolute and relative liver and thyroid weights were increased at $\geq$ 1000 ppm and absolute pituitary weights were decreased at 4000 ppm. Thyroid and pituitary (pars distalis) hypertrophy/hyperplasia were increased at $\geq$ 1000 ppm. T4 (L-thyroxine) was significantly decreased at 4000 ppm. Biliary levels (bile to plasma ratios, bile flow and bile clearance) were increased at 4000 ppm. Percent dose excreted as T4-glucuronide was increased at 4000 ppm. Hepatic UDP-glucuronosyltransferase activity with L-thyronine treatment was increased/mg protein and increased/gram of liver and per whole liver at 4000 ppm. Effects were shown to be reversible (body weights, food consumption, gross liver pathology, liver and thyroid weights and histopathology in pituitary and thyroid) in the "recovery" group. Hormone, enzyme and biliary excretion of 125-I label were generally decreased over control in this group.) These data are supplemental to 060-061/091888-091889. (Silva & Kishiyama, 9/13/93).

070 115340, "Pronamide (Kerb® Herbicide): Effects of Endocrine Regulation of the Testis in Rats - Pilot Study", (G.A. Hazelton, L.J. DiDonato, K.F. Donofrio and B.A. Kulwich, Rohm and Haas Toxicology Department, Report No. 90R-179, 12/6/91). Pronamide (purity = 96.4%) in diet was fed to male Crl: CD® BR rats (20/group) at 0 (acetone mixed with feed) or 4000 ppm for 13 weeks.

Alterations that may influence hormonal regulation of the testes occurred with increases in the following: serum concentrations (luteinizing hormone, follicle stimulating hormone and estradiol); testosterone oxidation capacity in liver microsomes; total p450 and cytochrome b5 content & activity of NADPH-cytochrome c reductase in the whole liver. The severity and incidence of hypertrophy/hyperplasia in the pituitary and the numbers of interstitial cells of the testes were also increased. **Possible adverse effect indicated: Hormone balance for testicular regulation is negatively affected. NOTE: These data are supplemental to study 060-061/091888-091889.** (Kishiyama & Silva, 9/15/93).

072 118047 Historical data were submitted by the registrant 7/11/92 to state that the hepatocellular carcinomas and adenomas in study 061/091889 were incidental and not related to propyzamide administration. DPR maintains that the lesions are compound-related in light of the tumors and related effects in liver that occur in most, if not all chronic and subchronic studies in more than one species. M. Silva, 2/24/94.

CHRONIC, DOG

** 062 089232, "Pronamide (Kerb® Technical Herbicide): 52 Week Oral (Dietary) Toxicity Study in the Beagle Dog", (J.P. Briffaux, Hazleton France (HF), HF Study No. 616/503, 2/20/91). Pronamide (Kerb® herbicide; technical), purity = 96.8%, was administered in the feed at concentrations of 0, 300, 875, or 1750 ppm to 6 Beagle dogs/sex/group for 52 weeks. NOEL = 300 ppm/12 mg/kg/day (Body weights at 1750 ppm were significantly lower than control in both sexes. Food consumption was also decreased throughout most of the study in both sexes. Platelet counts were significantly increased at 1750 ppm in females. Alkaline phosphatase, gamma glutamyl transpeptidase and alanine aminotransferase (females only) were significantly increased at 1750 ppm. Serum albumin was significantly decreased in both sexes at 1750 ppm. Adrenal weights, absolute & relative to brain weight--females and relative to body weight--both sexes were significantly increased at 1750 ppm. Liver weights absolute & relative to brain weight--females and relative to body weight--both sexes were increased at $\geq$ 875 ppm. Both sexes had liver histopathology at $\geq$ 875 ppm and kidney histopathology at 1750 ppm. (Kishiyama & Silva, 3/2/92).

066 111520 "Pronamide (Kerb® Technical Herbicide): 52 Week Oral (Dietary) Toxicity Study in the Beagle Dog," (Y. Guichard, Study Pathologist, Hazleton France (no date). This volume contains photomicrographs of liver and kidney histopathology from study 089232. The data are supplemental (no worksheet). M. Silva, 3/17/92.

062 089233. Range-finding Study for 089232. "Kerb® Herbicide - 4 Week Oral (Dietary Administration) Toxicity Study in the Beagle Dog", (J.P. Briffaux, Hazleton France (HF), HF Study No. 616/502, 2/11/91). Pronamide (Kerb* herbicide; technical), purity = 96.8% was administered in the feed at concentrations of 0, 1250, 2500 or 5000 ppm to 2 Beagle dogs/sex/group for 4 weeks. NOEL < 1250 ppm/day (Thymus weights, both absolute and relative, were decreased in both sexes at all doses. Relative liver weights were increased in both sexes at $\geq$ 2500 ppm. There was also decreased body weight and food consumption at $\geq$ 2500 ppm. Some clinical chemistry and hematological effects were observed at 5000 ppm.) This was range-finding for the definitive chronic dog study DPR # 089232). (Kishiyama & Silva, 2/25/92).

024, 046 036796, 066119, "Toxicologic Study on the Effect of Adding RH-315 to the Diet of Beagle Dogs (Two-Year Feeding Study)," (Department of Pharmacology, Medical College of Virginia, 6/13/68). FH-315 (lot no. SW-68-0261; purity = 97%) was fed in the diet at 0, 30, 100 or 300 ppm (4/sex/group) for 104 weeks (1/sex/group was sacrificed at 52 weeks). No adverse effect indicated. NOEL > 300 ppm (no significant effects were observed at any dose). This study was originally reviewed as unacceptable by J. Gee, 11/25/85 since it lacked an MTD (dose justification), an analysis of dose in the

diet, clinical observations and a tabulation of histopathology. An analysis of dose in the diet as well as information on stability, homogeneity and concentration verification was received by CDFA (Volume/record#: 046 066119) and found to be acceptable. The study remains UNACCEPTABLE, however, since there was no acceptable dose justification and no ophthalmological exam included in the report. The study is not upgradeable. (M. Silva, 9/28/88)

046 066119, This volume contains information about preparation of propyzamide in the diet as well as information on its stability, homogeneity and concentration in feed. It also contains information on the analysis of propyzamide technical.

011 961143 "Toxicologic Study on the Effect of Adding RH-315 to the Diet of Beagle Dogs For a Period of Three Months," (Department of Pharmacology, Medical College of Virginia, 1967). Propyzamide technical (RH-315, Lot no. WDW 10:75, purity = 100%) was administered in diet to beagle dogs (1/sex/group) for three months at 0, 450, 1350 and 4050 ppm. No adverse effect indicated. NOEL = 1350 (A decrease in weight gain, elevation in serum alkaline phosphatase and enlarged livers was observed in both sexes). There was no mortality nor were there hematological, urinalysis or histopathologic effects observed. This subchronic study is supplementary to 024 036796**.** (M. Silva, 9/29/88)

011 961152, Abbreviated version of 036796; (Oshita, Wong, 4/18/85).

ONCOGENICITY, MOUSE

**** 317 - 0113 215467** "Pronamide (Propyzamide): 18-Month Oncogenicity Study in CD-1 Mice (3 Parts)," (Stebbins, K.E., Brooks, K.J.; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; 11/22/04). Pronamide (95.9% pure) was fed in diet to CD-1 mice (50/sex/dose) at 0 (diet only), 5, 50 and 250 mg/kg/day for 18 months to evaluate the potential for oncogenicity. Concentrations were adjusted periodically to maintain doses for males and females. Actual intake was close to nominal. Systemic NOEL = 5 mg/kg/day (There were slight decreases in body weights in both sexes at 250 mg/kg/day. Increased absolute and relative spleen and adrenal weights at 250 mg/kg/day (M), absolute and relative liver weight gains at $\geq$ 50 mg/kg/day (both sexes) and absolute and relative kidney weights at $\geq$ 50 mg/kg/day (F) was observed. Gross effects on liver in both sexes, in kidneys (F) and in skin and subcutis (M) were observed at 250 mg/kg/day. Decreased amount of fat was observed at $\geq$ 50 mg/kg/day in females. There were non-neoplastic histopathological effects in livers of males at $\geq$ 50 mg/kg/day and in females at 250 mg/kg/day. There were non-histopathological effects observed in gallbladder, adrenal glands, heart and lungs of both sexes at 250 mg/kg/day and in lungs of females and salivary glands of males at 250 mg/kg/day. Possible adverse effect: There was an increased incidence in both hepatocytic adenomas and carcinomas at 250 mg/kg/day. Acceptable. (Silva, 1/31/05)

026 036798, "Eighteen Month Study on the Carcinogenic Potential of Kerb (RH-315) in Mice (31-78 Week Period)", (Depart. of Pharmacology, Medical College of Virginia, 8/30/74), Kerb Technical (batch SW 71/0225, 97% active ingredient); 125/sex/group fed 0, 1000, or 2000 ppm in diet for 78 weeks; positive controls DEN and AAF. **Adverse effect** indicated: increased incidence of liver neoplasms in males at 1000 and 2000 ppm. NOEL < 1000 ppm. UNACCEPTABLE (only 2 dose levels, no analysis of dosing material, very limited histopathology) (Van Way, Remsen (Gee) 11/25/85) Rebuttal information, 12-3-86, justifies dosage, but does not change status; histopathology still deficient. (J. Carlisle, 8-6-87)

011 916157; This is a 30 week interim report on 036798 (Oshita, Wong 4/18/85)

027 036799, "Kerb®: Chronic Toxicity Study in the Mouse", (MIT Animal Pathology Laboratory, Cambridge, MA., # 81RC-157, 8/10/82), combined-835-mouse, technical grade Kerb® 95-99%, lot no.

3874, fed in the diet to 42 males/group at 0 or 2500 ppm for 6 months; at 0, 20, 100, 500, or 2500 ppm to 42 males/group for 15 or 18 months and to 63 males/group for 24 months. **Adverse effects**: liver changes and oncogenicity reported. NOEL = 20 ppm. UNACCEPTABLE and not upgradable (deficiencies: use of male mice only, nominal versus analytical concentrations in diet) (Van Way, Remsen 11/25/85; Rebuttal information, 12-3-86, clarifies purpose of study, but does not change status; J. Carlisle, 8-6-87).

Conclusion: Although neither combined mouse study is acceptable, together they adequately address the issue of oncogenicity in mice, and fill the oncogenicity data gap. They do not qualify as combined studies although they provide useful chronic toxicity information. (J. Carlisle, 8-6-87)

REPRODUCTION RAT

** 059, 072, 081 091887, 118046, 131699 "Pronamide: Two-Generation Reproduction Study in Rats", (H.M. Solomon & W.R. Brown, Rohm & Haas Company, Toxicology Dept., Report No. 88R-257, 6/14/90). "Additional Data to Two Generation Reproduction Study in Rats," (O'Hara, G.P., Rohm & Haas Company, no date). "Pronamide: Two Generation Reproduction Study in Rats (88R-257): California Review of Final Report and Supplemental Data." Pronamide/propyzamide (Kerb* Technical, purity = 93.1%) was incorporated in the feed at concentrations of 0, 40, 200 or 1500 ppm and fed to 25 mated female Charles River Crl: CD*BR P1 and P2 rats/group (20 females in the P2 generation in the 40 ppm group). P1 rats received treated feed when approximately 42 days old and throughout premating (minimum of 10 weeks), mating, gestation and lactation. P2 rats received treated food after weaning (minimum of 15 weeks), throughout mating, gestation, and lactation. Reproductive NOEL > 1500 ppm (No reproductive effects observed at any dose). Parental NOEL = 200 ppm (Both generations showed decreased body weights and food consumption during premating--both sexes, as well as during gestation and lactation--females at 1500 ppm. Both sexes of both generations showed an increase in hypertrophy of centrilobular hepatocytes, follicular cell hypertrophy in thyroid and hypertrophy of zona glomerulosa cells in the adrenal gland at 1500 ppm.) Pup NOEL = 200 ppm (F1 pups showed a significant decrease in body weight on day 1 post partum.) Originally unacceptable (Silva, 3/6/92 & 2/22/94), however, after submission and review of the requested data, the study is now acceptable. M. Silva, 5/30/95.

028 036800, "Three Generation Reproduction Study on Rats Receiving RH-315 in Their Diet", (Depart. of Pharmacology, Medical College of Virginia, 4/10/70), RH-315 97% purity, lot no. SW-68-0261; 20/sex/group were fed in the diet 0, 30, 100, or 300 ppm over 3 generations, 2 litters/generation. No adverse effects are reported. NOEL > 300 ppm. UNACCEPTABLE and not upgradable (no analysis of diet for actual amount, no food consumption data, no justification of dose, incomplete histopathology, no MTD, fewer than 20 pregnant animals per group, no clinical observations). (Van Way, Remsen (Gee) 1/10/86).

034 051356, Additional information and/or explanations to support 028 036800, including test article characterization, individual animal data and dose selection criteria in response to deficiencies found in the initial review by J. Gee 1/10/86. Re-reviewed by J. Carlisle, 7/14/87. The Additional information led to no change in status.

011 961155, This is an abbreviated version of 036800 (Oshita, Wong 4/18/85).

TERATOLOGY, RAT

029 036801, "Effects of RH315 on the Fetal Development in Rats", (Food and Drug Research Laboratories Inc., Maspeth, N.Y., # 0512, 10/22/71), Kerb Technical Ref. SW-0225, no purity stated; in corn oil administered by gavage to 26 pregnant females/group at 0, 150, or 300 ppm from day 6

through 16 of gestation; Caesarean sections performed on day 20. No maternal or developmental adverse effects reported. UNACCEPTABLE and not upgradable (only 2 dose levels, no individual fetal data, no necropsy or clinical findings given, no analysis of dosing suspension) (VanWay, Parker 12/9/85)
A replacement study was due in April, 1987.

** 052 075559, "Kerb* Herbicide: Oral (Gavage) Developmental Toxicity Study in Rats", (Solomon, H.M. and Holtz, J.W., Jr., Rohm and Haas Company, Toxicology Department, Spring House, PA., report # 87R-003, 7/10/87). Kerb* (propyzamide, 94.2% pure, lot 4859) was administered on days 6 through 15 of gestation (day 0 = detection of sperm plug) by gavage at 0 (vehicle = aqueous methylcellulose), 5, 20, 80, and 160 mg/kg/day to mated Crl:CD*BR female rats (25/group). No adverse effect. Maternal NOEL = 20 mg/kg/day (A reduced maternal body weight gain was reported at 80 and 160 mg/kg/day). Developmental NOEL $\geq$ 160 mg/kg/day (no effects were observed at any dose). ACCEPTABLE. (H. Green & M. Silva, 8/29/90).

TERATOLOGY, RABBIT

Rangefinding Study:

317 - 030 036802 ARangefinding Teratology Study with Kerb in Rabbits,@ (Costlow, R.D., Kane, W.W.; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report #: 83R-025; Protocol #: 83P-063; 5/24/85). Propyzamide (Kerb, 96.8% pure) was administered by oral gavage to artificially inseminated New Zealand White rabbits (6/dose) at 0 (0.5% methylcellulose), 10, 31.6, 100, 215, 464 and 1000 mg/kg (limit test) during days 7 - 19 of gestation. Maternal NOEL = 10 mg/kg (At 100 and 215 mg/kg, mottled/congested liver and reddened gastric mucosa were observed. Abortions were treatment-related, secondary to maternal toxicity but not a direct effect on the conceptus (though a concommitant primary embryotoxic effect cannot be discounted according to the report) at 100 and 215 mg/kg. Abortions were not increased at 464 and 1000 mg/kg, since high maternal toxicity killed does before they could abort. Does at $\geq$ 215 mg/kg, had increased clinical signs (irregular feces, urine stained fur, red urine, anuria, soiled anal area, passiveness, ataxia, lethargy/prostration, discharge from nose/eyes, diarrhea, salivation). Body weights were significantly decreased from day 11 - 29 at $\geq$100 mg/kg. At $\geq$ 100 mg/kg, does had an increased incidence in periportal to midzonal punctate vacuolization, individual hepatocellular necrosis, pigmentation of Kupffer cells, periportal - midzonal hypertrophy, increased eosinophilia and cloudy swelling of hepatocytes. One doe at 31.6 mg/kg had peroportal punctate vacuolization.) Developmental NOEL = 31.6 mg/kg (**Possible adverse effect:** There was an increased incidence in resorptions at $\geq$ 100 mg/kg. The report considered propyzamide to be embryo-fetotoxic at $\geq$ 100 mg/kg.) These data are supplemental. Parker, 12/10/85 and Silva, 11/8/01.

Definitive Study:

** 317 - 030 036803 ATeratology Study with Kerb Technical (No Clay) in Rabbits,@ (Costlow, R.D., Kane, W.W.; Rohm and Haas Company, Toxicology Department, Spring House, PA; Report #: 83R-026; Protocol #: 83P-064; 6/4/85). Propyzamide (Kerb, 96.8% pure) was administered by oral gavage to artificially inseminated New Zealand White rabbits (18/dose) at 0 (0.5% methylcellulose), 5, 20 and 80 mg/kg during days 7 - 19 of gestation. The study was previously reviewed (Parker, 12/10/85) with a Maternal NOEL = 5 mg/kg and a Developmental NOEL > 80 mg/kg. Upon re-evaluation of developmental effects, the maternal NOEL remains at 5 mg/kg (At $\geq$ 20 mg/kg there was an increase in irregular feces, anorexia, red or white precipitate in the urine, blood and/or aborted material in the drop pan and hunched appearance. The drop in soiled anal area at 80 mg/kg was attributed to anorexia. Maternal body weights (days 11 - 20) and body weight gains (day 7 - 20) were significantly decreased at 80 mg/kg. Absolute and relative liver weights were increased at 80 mg/kg. There was an increased

incidence in late resorptions that went along with abortions at 80 mg/kg. At 80 mg/kg increased incidence in punctate vacuolated hepatocytes, swollen hepatocytes, hepatocellular necrosis, pigmentation of Kupffer cells and hepatocytes and eosinophilic hepatocytes occurred. At 80 mg/kg does with liver lesions were generally those that died prior to day 29 or those that aborted and were killed prior to day 29. Grossly mottled or dark liver corresponded to moderate or severe liver lesions in 5/5 cases at 80 mg/kg. In 3/13 livers which were grossly normal there were moderate or severe liver lesions.) The developmental NOEL, depending on how abortions and resorptions are interpreted may be considered to be 20 mg/kg (There was an increased incidence in late resorptions that went along with abortions at 80 mg/kg. There is no evidence to show that these effects are due to maternal toxicity or to direct embryo/fetotoxicity.) The study remains acceptable. Parker, 12/10/85 and Silva, 11/9/01

GENE MUTATION

031 036805, "Mutagenicity of Kerb (propyzamide) in Bacteria", (Japan Institute of Environmental Toxicology, 8/10/78), mutagenicity-842-Salmonella typhimurium and Escherichia coli, Kerb (propyzamide) 93.7%; dissolved in DMSO; reversion assay with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, TA100 and Escherichia coli WP2 hcr, 2 replicates, at 0, 10, 50, 100, 500, 1000, or 5000 ug/plate; with/without S9 rat liver fraction (Aroclor induced) activation; positive controls 2AA, AF-2, 2-nitrofluorene, beta-propiolactone, and 9-aminoacridine. No mutagenicity reported. UNACCEPTABLE and not upgradable (no repeat trial to verify findings). (Van Way, Remsen (Gee) 11/22/85).

034 51357, "Mutagenic Evaluation of Compound RH-315", (Litton Bionetics, Kensington, MD., # 2547, 8/29/75), RH-315, no purity stated; plate assay at 1, 10, 100, 500, or 1000 ug/plate with Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, or TA-100, with/without S9 mouse liver (Aroclor induced) activation; positive control with activation - DMNA, AAF, or DMBA, without activation - EMS, NF, or QM. Due to high cytotoxicity, data was not collected from the 1000 ug/plate group. No mutagenic activity reported. UNACCEPTABLE (no analysis of test solutions, no confirming trial). (Carlisle 7/13/87).

** 031 036807, "Gene Mutation in Chinese Hamster V79 Cells", (Life Science Research Roma Toxicology Centre, Rome, Italy, # 107001-M-02884, 10/29/84), Kerb Technical (no clay) 95.5-96.3%, lot no. 2-0801, TD no. 83-144; tested in 1% DMSO at 0, 2.5, 5, 10, 20, or 40 ug/ml with Chinese hamster V79 cells for HGPRT locus mutation with/without S9 rat liver (phenobarbitone and betanaphthoflavone induced) activation; 3 replicates; positive control +S9 = DMN, -S9 = EMS; cells were exposed for 3 hours. Expression times of 48, 96, and 168 hours. No increase in mutation frequency reported. ACCEPTABLE. (Van Way, Remsen (Gee) 11/25/85).

CHROMOSOME ABERRATION

011 916161, "Final Report, Cytogenetic Study, Kerb Technical" (Litton Bionetics, # 2380, 4/16/73), Kerb Technical, no purity stated, in methocel fed in the diet or dosed by intubation at 0, 5, 50, or 500 mg/kg, single dose daily for 5 days; 5 males/group; positive control TEM; sampled at 5 days, examined 250 cells/dose; no chromosomal aberrations reported. UNACCEPTABLE and not upgradable (no analysis of test article nor dosing solution, only 5 animals of one sex used, criteria for scoring aberrations not apparent, no individual data, no quality assurance) (Oshita, Wong 4/22/85).

011 961159, "Final Report, Cytogenetic Study, Kerb Analytical", (Litton Bionetics, Inc., # 2381, 4/16/73), chromosome-843-rat; Kerb analytical, no purity stated; in 0.5% methocel administered by gavage or fed in the diet at 0, 5, 50, or 500 mg/kg/day, 5 males/group; single daily dose for 5 days; positive control - TEM; sacrificed at 5 days, 250 cells/dose (200 cells in high dose due to 1 death). No chromosomal aberrations reported. UNACCEPTABLE and not upgradable (used analytical grade, no

test article purity stated, no dose justification, used only males and only 5 animals per dose, not clear which animals received which dosing method, no individual animal/chromosome data). (Green, Gee 8/6/87).

** 031 036806, "Kerb In Vivo Cytogenetic Study in Mice", (Rohm and Haas Co., Toxicology Department, Spring House, PA., # 84R-112, 10/31/85), Kerb technical (no clay) TD 83-144, 96.8% a.i., lot no. 2-0801; in 0.5% methylcellulose given in a single peroral dose or for 5 consecutive days intraperitoneally at 0, 0.48, 1.94, or 4.84 g/kg; 30 male mice/single dose group, 10 male mice/5 day group; TEM as positive control; sampled 10 animals/single dose group at 6, 24, and 48 hours, all animals/5 day group (except high-dose group due to excessive mortality) at 6 hours. No adverse effects reported. NOEL ~ 0.48 g/kg for clinical observations. Initially unacceptable (Van Way, Remsen (Gee) 11/22/85) (used only male mice, did not analyze dosing solution until 35 days later when found 62-77% of theoretical). Re-reviewed by J. Carlisle, 7/14/87. Information in 051358 allows upgrade to ACCEPTABLE with no adverse effects.

034 051358, Provides report on analysis of dosing materials, acute toxicology information for Kerb Flowable Herbicide, and explanations in response to the deficiencies found in the original review of 031 036806, by J. Gee, 11/22/85.

DNA DAMAGE

031 036804, "Mutagenicity of Kerb (Propyzamide) in Bacteria", (Japan Institute of Environmental Toxicology, 8/10/78), mutagenicity-844-Bacillus subtilis, Kerb (Propyzamide) 93.7%; dissolved in DMSO; recombination assay with Bacillus subtilis M45 (Rec^-) and H17 (Rec^+) at 0, 20, 100, 200, 500, 1000, or 2000 ug/disk, negative control-Kanamycin, positive control-Mitomycin C. No **selective inhibition of the rec**^{7} strain reported. UNACCEPTABLE, not upgradable (deficiencies: maximum of 2000 ug/disk with no rationale for not going higher, no activation series, no repeat trial). (Van Way, Remsen (Gee) 11/22/85).

** 047 071734, "Kerb* Technical In Vitro Unscheduled DNA Synthesis Assay", (Muller, G. and Frank, J.P., Rohm and Haas Company, Toxicology Department, Spring House, PA., report No. 86R-185, 2/11/87). Kerb* (propyzamide) technical (94.2% pure, lot # 4859) was used in a 19 hour-exposure of primary rat hepatocytes (3 replicates/group) at 0.1, 0.5, 1.0, 5.0, 10.0, 25.0, 50.0, 100.0, and 500.0 ug/ml for UDS determination (autoradiography, 50 cells scored/replicate and 150 total cells/dose were scored). Reduced cell survival at 100.0 and 500.0 ug/ml (48% and 40% of solvent control values respectively) was observed. No UDS effect. ACCEPTABLE. (H. Green & M. Silva, 8/27/90).

NEUROTOXICITY

Not required at this time.